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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/757,803	MCSWIGGEN ET AL.	
	Examiner	Art Unit	
	Amy H. Bowman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 March 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18-20 and 33-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18-20 and 33-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 January 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

Applicant's response filed 3/25/08 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 10/30/07 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 18-20 and 33-38 are pending in the application.

Applicant's arguments and/or amendments filed 3/25/08, with respect to the rejection under 35 USC 112, have been fully considered and are persuasive. Therefore, this rejection has been withdrawn. However, the rejections below are pending as explained below.

Priority

The instant claims are accorded the priority date of 2/20/2002, which is the filing date of application 60/358,580, because application PCT/US03/05346 and application 60/358,580 each teach each of the limitations of claims 18-20 and 33-38.

Response to Arguments--Claim Rejections - 35 USC § 103

Claims 18-20 and 33-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Elbashir et al. (The EMBO Journal, 2001, Vol. 20, No. 23, pages 6877-6888), in view of Matulic-Adamic et al. (US 5,998,203), Parrish et al. (Molecular Cell, Vol. 6, pages 1077-1087, 2000), and Crooke (US 5,898,031), for the reasons of record set forth in the office action mailed on 12/21/06, the advisory actions mailed on 3/27/07 and 5/1/07, the office action mailed on 10/30/07, and as explained below.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The invention of the above claims is drawn to a chemically modified double stranded nucleic acid comprising a sense strand and an antisense strand, wherein each

strand is 18 to 27 nucleotides in length, 18 to 23 nucleotides of each strand are complementary to each other, and at least 18 nucleotides of the antisense strand are complementary to a target RNA sequence, and the sense strand comprises a terminal cap moiety at the 5' and 3' end and the antisense strand optionally includes a terminal cap moiety at the 3' end. The invention is further drawn to specific terminal cap moieties, as well as modifications to the duplex and a composition comprising the double stranded nucleic acid and a pharmaceutically acceptable carrier or diluent.

Elbashir et al. (EMBO) teach siRNAs, wherein each strand is 21-23 nucleotides in length and wherein at least 19 nucleotides of the sense strand are complementary to the antisense strand. Elbashir et al. teach chemical modification with 2'-deoxy or 2'-O-methyl modifications. Elbashir et al. teach modification of 19% of the nucleotides of a duplex 21 nucleotides in length with 2'-deoxy modifications.

Elbashir et al. teach duplexes with 2 nt 3' overhangs, as well as blunt ended duplexes wherein all 21 nucleotides are complementary between the sense and antisense strand. Elbashir et al. teach that duplexes 21 nucleotides in length with 2 nt 3' overhangs were the most efficient triggers of sequence-specific mRNA degradation. Elbashir et al. teach duplexes wherein the sense and antisense strands are complementary at 19 or 21 nucleotide positions (see for example, Figure 1D (1st duplex) and Figure 1F (1st duplex)). Elbashir et al. teach 2'-deoxythymidine in the 3' overhang (see page 6884). The 100% modified duplex taught by Elbashir et al. is considered to not comprise ribonucleotides.

Elbashir et al. do not teach double stranded nucleic acid molecules comprising the instantly recited terminal cap moieties and do not teach 2'-deoxy-2'-fluoro modifications. Elbashir et al. do not teach a composition comprising the double stranded nucleic acid molecule and a pharmaceutically acceptable carrier.

Matulic-Adamic et al. teach chemical modifications of double stranded nucleic acid structures. The enzymatic RNA molecules of Matulic-Adamic et al. are taught to be targeted to virtually any RNA transcript and achieve efficient cleavage (see column 1) and to be sufficiently complementary to a target sequence to allow cleavage. Matulic-Adamic et al. teach the incorporation of chemical modifications at the 5' and/or 3' ends of the nucleic acids to protect the enzymatic nucleic acids from exonuclease degradation, which improves the overall effectiveness of the nucleic acid, as well as facilitates uptake of the nucleic acid molecules (see column 2). Matulic-Adamic et al. teach base, sugar and/or phosphate modification, as well as terminal cap moieties at the 5'-cap, 3'-cap, or both. Specifically, 3' phosphorothioates, inverted abasic moieties, and 2'-O-methyl modifications are utilized. Matulic-Adamic et al. teach 2'deoxy nucleotides and 2'-deoxy-2'-halogen nucleotides, wherein Br, CL and F are representative halogens (see column 3, for example). For example, figure 3 contains a ribozyme structure that encompasses modification of at least 20%, at least 30%, at least 40% or at least 50% of the nucleotide positions, as well as the modifications instantly claimed. The modifications can be in one or both of the strands and can be modifications of different types within the same structure.

Matulic-Adamic et al. teach that preferred caps include 4', 5'-methylene nucleotides, 1-(beta-D-erythrofuranosyl) nucleotides, 4'-thio nucleotides, 1,5-anhydrohexitol nucleotides, L-nucleotides, threo-pentofuranosyl nucleotides, acyclic 3', 4'-seco nucleotides, 3,4-dihydroxybutyl nucleotides, 3,5-dihydroxypentyl nucleotides, 3'-3'-inverted nucleotide moieties, 3'-3'-inverted abasic moieties, 3'-2'-inverted nucleotide moieties, 3'-2'-inverted abasic moieties, 5'-5'-inverted nucleotide moieties, and 5'-5'-inverted abasic moieties (see columns 3 and 4, for example). Matulic-Adamic et al. teach compositions comprising the nucleic acid and reaction buffer, which is a diluent.

Parrish et al. teach a chemically synthesized siRNA molecule, wherein each strand is 26 bp in length. Additionally, Parrish et al. teach a 742 nt long dsRNA with extensive modification with 2'-deoxy-2'-fluoro modifications, which resulted in successful RNA interference. Parrish teaches that the 2'-deoxy-2'-fluoro modifications incorporated into the long dsRNA produces unc-22 interference and furthermore described the interference as strong (+++, see figure 5).

Crooke teaches gapmer oligonucleotide chemistry and teaches that gapmer strategies increase oligonucleotide affinity to the target RNA (see column 9, for example). Crooke teaches chemical modifications that are incorporated to improve pharmacokinetic binding, absorption, distribution or clearance properties of the compound, affinity or specificity of the compound to target RNA, or modification of the charge of the compound (see column 7, for example).

Crooke teach that a particularly useful 2'-substituent group for increasing the binding affinity is the 2'-fluoro group (see column 12). Crooke also teaches 2'-O-methyl modifications.

It would have been obvious to synthesize a double stranded nucleic acid molecule with the structural characteristics taught by Elbashir et al., wherein the molecule is formulated in a composition with a diluent, as taught by Matulic-Adamic et al. It would have been obvious to incorporate the specific modifications taught by Parrish et al. and Matulic-Adamic et al.

One would have been motivated to synthesize a double stranded nucleic acid molecule, as taught by Elbashir et al. (EMBO), wherein the molecule is formulated in a composition with a diluent, because Matulic-Adamic et al. teach successful inhibition of target gene expression with nucleic acid molecules formulated in a diluent. Furthermore, the reactions performed by Elbashir et al. require diluents such as buffers and water.

One would have been motivated to synthesize a double stranded nucleic acid molecule, as taught by Elbashir et al. (EMBO), with the modifications taught by Parrish et al. and Matulic-Adamic et al. because each of the modifications were known in the art to protect nucleic acids from exonuclease degradation, which improves the overall effectiveness of the nucleic acid, as well as facilitates uptake of the nucleic acid molecules, as taught by Matulic-Adamic et al. Additionally, Parrish et al. and Matulic-Adamic et al. teach extensive chemical modification of long dsRNA and ribozymes, respectively, with successful inhibition of target gene expression.

Since Elbashir et al. (EMBO), Matulic-Adamic et al., and Parrish et al. teach modified double stranded nucleic acid molecules that inhibit target gene expression, and Crooke teaches gapmer oligonucleotide chemistry to improve pharmacokinetic properties of the oligonucleotide, one would have been motivated to synthesize duplexes, as taught by Elbashir et al., with each of the instantly recited modifications, as taught by Elbashir et al., Matulic-Adamic et al., and Parrish et al. in order to optimize the activity of the molecule, as taught by Crooke.

Additionally, antisense oligonucleotides, ribozymes, and dsRNAs are each commonly used for sequence-specific mRNA knockdown and each of these encounters delivery problems for effective application. Therefore, one would have been motivated to utilize the same modifications and techniques that have been utilized to overcome these problems with antisense oligonucleotides or ribozymes with siRNAs to add the same benefits to RNAi technology.

For example, Crooke teaches that gapmer oligonucleotide chemistry has provided antisense oligonucleotides with increased target affinity and pharmacokinetic properties. Crooke teaches that different modifications at different regions of the oligonucleotide have been tested in order to optimize oligonucleotide activity. Crooke teaches stepwise experimentation of modifications throughout oligonucleotides in order to find the optimal configuration. Crooke is relied upon as evidence that it is common to experiment with different known modifications at different locations to optimize oligonucleotide activity.

It would have been prima facie obvious to perform routine optimization to determine which of the known modifications or combinations of modifications are optimal. As noted in *In re Aller*, 105 USPQ 233 at 235,

> More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Routine optimization is not considered inventive and no evidence has been presented that the selection of the specific modifications used were other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art.

Therefore, one would have been motivated to apply such a method to incorporate known modifications at various locations and amounts, as taught by Crooke, into the siRNA duplexes that were synthesized by Elbashir et al.

Finally, one would have a reasonable expectation of success given that each of the modifications were known in the art at the time the invention was made to add benefits to antisense oligonucleotides, ribozymes, dsRNAs or siRNA duplexes, as evidenced by Elbashir et al., Matulic-Adamic et al., Parrish et al. and Crooke, wherein each of the molecules face the same challenges, and each of which can be improved with modifications. Since Crooke teaches effectively walking modifications across antisense oligonucleotides to optimize the location of the modifications and activity of the oligonucleotide and Elbashir et al., Matulic-Adamic et al., and Parrish et al. teach successfully synthesizing modified double stranded nucleic acid molecules, one would

reasonably expect for each of the modifications to benefit the double stranded nucleic acid molecules of Elbashir et al. as well. Furthermore, the long chemically modified dsRNA taught by Parrish et al. further demonstrate that extensively modified dsRNA molecules result in RNA interference activity. Since Elbashir et al., Matulic-Adamic et al., and Parrish et al. teach modification of double stranded nucleic acid molecules and Crooke teaches experimentally determining optimal locations and levels of modification of antisense oligonucleotides, incorporating each of the modifications in the double stranded nucleic acid molecules of Elbashir et al. is considered within the realm of routine optimization.

It is noted that Elbashir et al. teach that 100% modification of one or both strands with 2'-deoxy or 2'-O-methyl modifications abolished activity. However, regardless of the results of these specific modifications at 100% of the positions of one or both strands, Elbashir et al. did modify duplexes and published data regarding successful inhibition with some duplexes and unsuccessful inhibition with others, supporting that testing of such known chemical modifications is routine in the art. The results of Elbashir et al. are considered to offer motivation to incorporate chemical modifications at various percentages to optimize the activity of the duplex because not all modifications result in activity at every percentage.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Applicant asserts that Elbashir does not teach terminal caps at all. Applicant traverses that position taken by the examiner that the chemically modified terminal nucleotides of the siRNA duplexes of Elbashir et al. meet the instant limitation of terminal caps because “terminal cap” is not a term of the art and has not been defined in the instant specification. Applicant asserts that the instant specification does in fact define the term “terminal cap” and points to locations in the specification wherein different embodiments are disclosed. Contrary to applicant's assertion, the specification does not set forth a definition for the term "terminal cap". The examples of terminal caps in the specification are not a definition as asserted by applicant. Applicant asserts that the terminal cap serves to protect the loading of a capped sequence from the capped end into the RISC complex.

In lack of a closed definition of the term “terminal cap”, the modifications of the terminal nucleotides of Elbashir et al. meet the instant limitation of "terminal cap". However, as set forth in the instant rejection under 35 U.S.C. 103(a) above, Elbashir et al. does not teach the instantly recited terminal caps of claim 18 and therefore does not anticipate the claims, hence the rejection under 35 U.S.C. 103 rather than 35 U.S.C. 102. However, Matulic-Adamic et al. teaches a multitude of terminal cap moieties that anticipate the instantly recited terminal cap moieties, but teach incorporation into ribozymes rather than double stranded nucleic acid molecules with the instant structure. Since Matulic-Adamic et al. teach that incorporation of chemical modifications at the 5’ and/or 3’ ends of the nucleic acids protect the enzymatic nucleic acids from exonuclease degradation, which improves the overall effectiveness of the nucleic acid,

as well as facilitates uptake of the nucleic acid molecules, one would have been motivated and it would have been obvious to try the specific terminal cap moieties of Matulic-Adamic et al. in the siRNA duplexes of Elbashir et al. because each were known to desire benefits that are achieved with chemical modifications, as evidenced by the teachings of both. Although applicant asserts that the intention of the instant terminal caps is to protect the loading of a capped sequence from the capped end into the RISC complex, the motivation to try the terminal cap moieties does not need to be for the same reason as the instant motivation.

Applicant asserts that Elbashir et al. only modifies the 3' overhangs, rather than the 5' and 3' ends of the sense strand and optionally the 3'-end of the antisense strand, as instantly recited. Elbashir et al. was not relied upon for directly teaching the configuration of modification that is instantly recited, but was rather relied upon for teaching double stranded chemically modified nucleic acid molecules within the instant size range. Although applicant asserts that Matulic-Adamic et al. does not add anything because the structures are ribozymes rather than the instantly recited molecules, Matulic-Adamic et al. certainly adds motivation to incorporate the terminal cap moieties taught by Matulic-Adamic et al. One would have been motivated to incorporate the modifications of Matulic-Adamic et al. into the siRNA molecules of Elbashir et al., as each are sequence specific nucleic acid inhibitory molecules that each face delivery challenges, wherein it was known to test the same types of chemical modifications in each type of molecule to optimize the activity therein. Although the molecules of Matulic-Adamic et al. do not have an identical structure to the molecules of Elbashir et

al., one would have been motivated to optimize the activity of the molecules of Elbashir et al. via testing incorporation of the terminal cap moieties of Elbashir et al. at different locations, particularly in view of the teachings of Crooke, who teaches testing various locations of a nucleic acid for optimal activity with chemical modifications.

Furthermore, since Matulic-Adamic et al. teach terminal cap moieties at the 5'-cap, 3'-cap, or both, one would have been motivated to try different combinations within the molecules of Elbashir et al.

The instant specification discloses a multitude of oligonucleotide and ribozyme art regarding chemical modifications and teaches that "Such publications describe general methods and strategies to determine the location of incorporation of sugar, base and/or phosphate modifications and the like into nucleic acid molecules without modulating catalysis, and are incorporated by reference herein. In view of these teachings, similar modifications can be used as described herein to modify the siNA nucleic acid molecules of the instant invention so long as the ability of siNA to promote RNAi in cells is not significantly inhibited." (see page 112).

It is acknowledged that the specification is not to be relied upon for a source of motivation and that is not considered to be the instant case. The specification is merely being relied upon to distinguish that applicant recognized that double stranded nucleic acid modification is dependent upon the state of the art of oligonucleotides and ribozymes and that previously beneficial chemical modifications would be used with double stranded nucleic acid molecules as well. Testing of optimal location of such

modifications is within the realm of routine optimization, as evidenced by the combined teachings of the instantly recited references.

Applicant argues that Parrish et al. does not teach terminal cap moieties. It is noted that Parrish et al. was not relied upon for such a teaching, but rather for teaching incorporation of 2'-deoxy-2'-fluoro modifications in dsRNA molecules that resulted in strong interference, thus offering motivation to incorporate "one or more 2'-deoxy-2'-fluoro pyrimidine nucleotides" in the sense or antisense strand, as instantly recited in claims 35 and 36, respectively.

Applicant argues that Crooke et al. does not teach the instant configuration. However, Crooke et al. was not relied upon for such a teaching but was rather relied upon as evidence that testing is routine in the art to walk modifications across nucleic acid molecules to optimize the activity therein.

Applicant argues that the rejection is largely based on the modifications of the dependent claims, rather than the terminal cap moieties required by instant claim 1. It is assumed that applicant is referring to claim 18, the independent claim. The rejection is based upon the obviousness of the terminal cap moieties of claim 18, as well as the obviousness of the modifications of the dependent claims. The terminal cap moieties, as well as positioning of the terminal cap moieties is obvious in view of the combined teachings of Elbashir et al. regarding siRNA duplexes; Matulic-Adamic et al. regarding teachings of the instant caps and benefits thereof; and Crooke et al. that offers motivation to test at various locations of a nucleic acid for optimal activity. The modifications of the dependent claims are obvious in view of the combined teachings of

all of the instantly cited teachings, as it was known to incorporate each type of modification into nucleic acid inhibitory molecules to increase the stability of the molecule.

Furthermore, one of skill in the art would reasonably expect for the modifications of Matulic-Adamic et al. to likely benefit the molecules of Elbashir et al. as well. As explained above, the motivation need not be the same motivation set forth by applicant, but rather the motivation to enhance the stability of the molecules as set forth by Matulic-Adamic et al. Elbashir et al. teaches that preferred molecules are modified in the terminal regions. Therefore, one would reasonably expect for the terminal cap moieties of Matulic-Adamic et al. to enhance the stability of the molecules of Elbashir et al. as well.

It is noted that the instant broad claim 18 only requires a terminal cap moiety at the 5'- and 3'-ends of the first strand, and an optional 3'-end terminal cap on the second strand. The dependent claims further require one or more of a type of chemical modification. This level of modification would certainly be considered obvious in view of the successful modifications of Elbashir et al. and Parrish et al. combined with the teachings of the instant types of terminal caps of Matulic-Adamic et al.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct

from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 18-20 and 33-38 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 15-18, 32, 36-40, 42-44, and 46-51 of copending Application No. 10/667,271. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are directed to chemically modified double stranded nucleic acid molecules with overlapping structural characteristics and modifications. The instant molecules are not designed to be targeted to any specific target RNA sequence and are therefore anticipated by the claims of application '271 that recite molecules with overlapping structural characteristics that are targeted to HCV RNA.

Application '271 recites double stranded nucleic acid molecules directed to HCV RNA, wherein the molecules comprise a sense and an antisense strand, wherein each strand is 18 to 27 nucleotides in length. Application '271 recites 2'-deoxy, 2'-deoxy-2'-fluoro, and 2'-O-methyl modifications at varying amounts in one or both strands, as well as terminal cap moieties including inverted deoxy abasic moieties and LNA nucleotides.

Application '271 recites terminal cap moieties at the 5'-end, 3'-end or both ends of the sense strand. Application '271 recites a composition comprising the nucleic acid molecule in a pharmaceutically acceptable carrier or diluent. Therefore, the instant claims are obvious in view of the claims of application '271.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 18-20 and 33-38 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-9, 13-20, and 23-29 of copending Application No. 10/664,668. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are directed to chemically modified double stranded nucleic acid molecules with overlapping structural characteristics and modifications. The instant molecules are not designed to be targeted to any specific target RNA sequence and are therefore anticipated by the claims of application '668 that recite molecules with overlapping structural characteristics that are targeted to VEGFr2 RNA.

Application '668 recites double stranded short interfering nucleic acid molecules directed to VEGFr2 RNA, wherein the molecules comprise a sense and an antisense strand, wherein each strand is about 19 to about 21 nucleotides in length. Application '668 recites 2'-deoxy, 2'-deoxy-2'-fluoro, and 2'-O-methyl modifications at varying amounts in one or both strands, as well as terminal cap moieties including inverted

deoxy abasic moieties. Therefore, the instant claims are obvious in view of the claims of application '668.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 18-20 and 33-38 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 3, 13-20, 31, 36-38, and 40-45 of copending Application No. 10/576,690. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are directed to chemically modified double stranded nucleic acid molecules with overlapping structural characteristics and modifications. The instant molecules are not designed to be targeted to any specific target RNA sequence and are therefore anticipated by the claims of application '690 that recite molecules with overlapping structural characteristics that are targeted to NOGO receptor RNA.

Application '690 recites double stranded nucleic acid molecules directed to NOGO receptor RNA, wherein the molecules comprise a sense and an antisense strand, wherein each strand is 18 to 27 nucleotides in length. Application '690 recites 2'-deoxy, 2'-deoxy-2'-fluoro, and 2'-O-methyl modifications at varying amounts in one or both strands, as well as terminal cap moieties including inverted deoxy abasic moieties and LNA nucleotides. Application '690 recites terminal cap moieties at the 5'-end, 3'-end or both ends of the sense strand. Application '690 recites a composition comprising

the nucleic acid molecule in a pharmaceutically acceptable carrier or diluent. Therefore, the instant claims are obvious in view of the claims of application '690.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 18-20 and 33-38 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-10 and 13 of copending Application No. 11/684,465. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are directed to chemically modified double stranded nucleic acid molecules with overlapping structural characteristics and modifications. The instant molecules are not designed to be targeted to any specific target RNA sequence and are therefore anticipated by the claims of application '465 that recite molecules with overlapping structural characteristics that are targeted to APP RNA.

Application '465 recites double stranded nucleic acid molecules directed to APP RNA, wherein the molecules comprise a sense and an antisense strand, wherein each strand is about 18 to about 27 nucleotides in length. Application '465 recites 2'-deoxy, 2'-deoxy-2'-fluoro, and 2'-O-methyl modifications at varying amounts in one or both strands, as well as terminal cap moieties including inverted deoxy abasic moieties. Application '465 recites terminal cap moieties at the 5'-end, 3'-end or both ends of the sense strand. Application '465 recites a composition comprising the nucleic acid

molecule in a pharmaceutically acceptable carrier or diluent. Therefore, the instant claims are obvious in view of the claims of application '465.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 18-20 and 33-38 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 3, 7-14, 19, 20, 23, 26, 28, 86, and 88-91 of copending Application No. 11/369,108. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are directed to chemically modified double stranded nucleic acid molecules with overlapping structural characteristics and modifications. The instant molecules are not designed to be targeted to any specific target RNA sequence and are therefore anticipated by the claims of application '108 that recite molecules with overlapping structural characteristics that are targeted to a RNA transcript, more specifically transcripts encoded by viral genes, more specifically HCV.

Application '108 recites double stranded nucleic acid molecules directed to an RNA transcript, wherein the molecules comprise a sense and an antisense strand, wherein each strand is 18 to 27 nucleotides in length. Application '108 recites 2'-deoxy, 2'-deoxy-2'-fluoro, and 2'-O-methyl modifications at varying amounts in one or both strands, as well as terminal cap moieties including inverted deoxy abasic moieties. Application '108 recites terminal cap moieties at the 5'-end, 3'-end or both ends of the sense strand. Application '108 recites a composition comprising the nucleic acid

molecule in a pharmaceutically acceptable carrier or diluent. Therefore, the instant claims are obvious in view of the claims of application '108.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 18-20 and 33-38 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-9, 13-20, 23-29, and 31-35 of copending Application No. 10/567,888. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are directed to chemically modified double stranded nucleic acid molecules with overlapping structural characteristics and modifications. The instant molecules are not designed to be targeted to any specific target RNA sequence and are therefore anticipated by the claims of application '888 that recite molecules with overlapping structural characteristics that are targeted to a XIAP RNA.

Application '888 recites double stranded nucleic acid molecules directed to an XIAP RNA transcript, wherein the molecules comprise a sense and an antisense strand, wherein each strand is about 18 to about 23 nucleotides in length. Application '888 recites 2'-deoxy, 2'-deoxy-2'-fluoro, and 2'-O-methyl modifications at varying amounts in one or both strands, as well as terminal cap moieties including inverted deoxy abasic moieties. Application '888 recites terminal cap moieties at the 5'-end, 3'-end or both ends of the sense strand. Application '888 recites a composition comprising the nucleic

acid molecule in a pharmaceutically acceptable carrier or diluent. Therefore, the instant claims are obvious in view of the claims of application '888.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 18-20 and 33-38 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 33-50 of copending Application No. 10/923,536. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are directed to chemically modified double stranded nucleic acid molecules with overlapping structural characteristics and modifications. The instant molecules are not designed to be targeted to any specific target RNA sequence and are therefore obvious in view of the claims of application '536 that recite molecules with overlapping structural characteristics.

Application '536 recites double stranded nucleic acid molecules that comprise a sense and an antisense strand, wherein each strand is about 15 to about 30 nucleotides in length. Application '536 recites 2'-deoxy, 2'-deoxy-2'-fluoro, 2'-O-methyl, and LNA modifications at varying amounts in one or both strands, as well as terminal cap moieties including inverted deoxy abasic moieties. Application '536 recites terminal cap moieties at the 5'-end, 3'-end or both ends of the sense strand and the 3' end of the antisense strand. Application '536 recites a composition comprising the nucleic acid

molecule in a pharmaceutically acceptable carrier or diluent. Therefore, the instant claims are obvious in view of the claims of application '536.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicant replied that they will consider filing one or more terminal disclaimers, if appropriate, when the claims are otherwise in final, allowable form.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy H. Bowman whose telephone number is (571)272-0755. The examiner can normally be reached on Monday-Thursday 6:00 - 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on (571) 272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Amy H Bowman
Examiner
Art Unit 1635

AHB

/J. E. Angell/
Primary Examiner, Art Unit 1635